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The Treatment of Plaque Psoriasis in the Pre- and Post-Biologic Era: Part I— Traditional Treatment Options for Psoriasis

Raptiva® (efalizumab) Treatment of Patients Who Respond Inadequately to Anti-Tumor Necrosis Factor Therapy

The Ratio of Physician Assistants to Supervising Physicians

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Dear Physician Assistant:

We proudly present the latest issue of our professional development newsletter **Derm PA Today** that speaks directly to you, the dermatology physician assistant. This newsletter is designed to include articles on topics that are timely and relevant to the day-to-day practice of the busy dermatology PA.

In this issue's cover story, Terry Arnold, MA, PA-C, Tulsa, OK, discusses the treatment of psoriasis in the pre- and post-biologic era in Part I of this two-part article on treatment options for psoriasis.

In addition, Leon Kircik, MD, Associate Clinical Professor of Dermatology, Indiana University Medical Center, Louisville, KY, describes the use of Raptiva® (efalizumab) for treatment of patients with chronic, moderate-to-severe plaque psoriasis who respond inadequately to anti-tumor necrosis factor therapy.

Finally, Jane Mast, PA-C, from Space Coast Dermatology, Merritt Island, FL, addresses the state laws and regulations regarding the ratio of PAs to supervising physicians.

Thank you for reading the latest installment of **Derm PA Today**. Our goal is to provide you with professional development through informative articles, as well as the latest developments in psoriasis treatment.

If you know of any of your colleagues who are not receiving **Derm PA Today** and would like to receive it for free, please call the Publisher, Joe Morris, at (800) 237-7285, ext. 204, or e-mail him at jmorris@hmpcommunications.com.

Best regards,



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The Treatment of Plaque Psoriasis in the Pre- and Post-Biologic Era: Part I— Traditional Treatment Options for Psoriasis

By Terry Arnold, MA, PA-C

Biologic agents were first introduced in 2003, ushering in a new era for treating patients with moderate-to-severe plaque psoriasis. Prior to that point, treatment options included topical agents, ultraviolet (UV) light therapy, and traditional systemic agents such as methotrexate, cyclosporine, and acitretin. While these treatments had varying degrees of effectiveness, they each suffered from different limitations. In Part I of this two-part series on psoriasis treatments, we will look at several different forms of therapy in the pre-biologic age. In the next edition of *Derm PA Today*, we will evaluate the approved biologic therapies for treating psoriasis, and how they can be utilized in clinical practice.

TOPICAL AGENTS

Topical agents such as corticosteroids, calcipotriene, tazarotene, anthralin, tar, and others have been widely used for many years. However, they are rarely beneficial to patients with diffuse forms of psoriasis. They are time-consuming to apply, messy, odoriferous, and often irritating.

Topical steroids have long been a mainstay of psoriasis therapy, and continue to be so. They have well-known benefits and many adverse effects, including the potential to induce skin atrophy, telangiectasia, striae, and tachyphylaxis with long-term use. They can be useful as an adjunct to systemic, light, or biologic therapies, but are rarely useful as monotherapy for moderate-to-severe disease.

Calcipotriene is a vitamin D analog approved for treatment of chronic plaque psoriasis. Although its onset of action is somewhat slower than topical steroids, it can be effective for long-term use as a steroid-sparing agent. Use can be limited by its potential to cause skin irritation, and also its cost. The primary concern with this vitamin D agent is the potential to induce hypercalcemia. For this reason, it is recommended that use be limited to less than 100 g per week.

Topical tazarotene can be used to reduce the induration and scale of psoriatic

plaques, but also causes significant retinoid irritation, frequently requiring concomitant treatment with topical steroids. Tazarotene is a pregnancy Category X medication, and should be avoided in women of child-bearing potential who are not using contraception.

Tar and anthralin are older topicals that are rarely used in contemporary dermatology. They are both quite irritating, odoriferous, and cause staining of the skin, hair, nails, and clothing. In the pre-biologic era, these topicals were used in combination with UV light treatments in the Goeckerman (coal tar + UVB) and Ingram (anthralin + coal tar baths + UV light) regimens.

UV LIGHT THERAPY

Ultraviolet light in the form of narrow-band UVB, UVA, and psoralen + UVA (PUVA) is effective for treating widespread psoriasis. Yet, these treatments can be difficult because of frequent office visits (2-3 times per week) and limited availability in certain geographic areas. Their onset of action is also relatively slow and frequently requires maintenance treatment. There is also significant risk for inducing cutaneous squamous cell carcinomas and possibly melanoma with PUVA. A safer option is the use of narrow-band UVB at a wavelength of 311 nm, which is still therapeutic for psoriasis but significantly less carcinogenic.

TRADITIONAL SYSTEMIC AGENTS

Traditional systemic agents have been extensively used by dermatologists since the early 1970s. Methotrexate, a chemotherapy agent, is particularly useful for moderate-to-severe plaque psoriasis, and also has utility in managing psoriatic joint disease. The drug has numerous interactions, multiple side effects, extensive laboratory monitoring, and end-organ toxicity. Long-term use of the drug also necessitates liver biopsy after a cumulative dose of 2.5 g.

Cyclosporine is another systemic agent that was originally formulated as an immunosuppressant in organ transplant. It has a relatively fast onset of action, but has

the potential to induce hypertension and nephropathy. There are also concerns of lymphoma with long-term use of this immunosuppressant.

Acitretin is the only once-daily oral medication that is FDA-approved for the treatment of psoriasis. It is an effective and convenient form of treatment for many patients. It does require regular lab monitoring and office visits, and has several common side effects (eg, cheilitis, alopecia, xerosis, headaches). It is also pregnancy Category X and should not be used by women who are pregnant, or may become pregnant during therapy or at any time for a period of 3 years after the drug is discontinued. Acitretin is a metabolite of etretinate (a drug withdrawn from the U.S. market in 1998), and major fetal abnormalities have been reported with both drugs. In fact, when acitretin is combined with ethanol, it is converted to etretinate, which carries a lifetime risk of teratogenicity. For this reason, women taking acitretin should not consume alcohol during treatment and for 2 months after treatment cessation.

CONCLUSION

The pre-biologic era of psoriasis offered numerous treatment options. While these treatments were effective and beneficial to many patients, they each suffered from different drawbacks. They are still very widely used, and likely will be for years to come. However, the new age of biologic treatments offers several advantages in terms of efficacy, convenience, and safety. In the second part of this series, we will look more closely at these new biologic options, and how to effectively integrate them into your clinical practice. ●●●



Terry Arnold is employed by Dr. Jeff Alexander in private practice in Tulsa, OK.

The opinions expressed in this article are those of the author and are not necessarily those of Genentech, Inc.

Raptiva[®] (efalizumab) Treatment of Patients Who Respond Inadequately to Anti-Tumor Necrosis Factor Therapy

By Leon Kircik, MD

Patients with psoriasis now have hope: Several biologic therapies are either currently approved or are being developed for the management of chronic, moderate-to-severe psoriasis. Clinical studies have demonstrated the overall safety and efficacy of three therapies—efalizumab (Raptiva[®]), alefacept (Amevive[®]), and etanercept (Enbrel[®])—all of which have received FDA approval for the treatment of patients with chronic, moderate-to-severe plaque psoriasis. In addition, Enbrel is FDA-approved for the treatment of patients with psoriatic arthritis. Two other agents, infliximab (Remicade[®]) and adalimumab (Humira[®]), are in late-stage clinical studies for chronic, moderate-to-severe plaque psoriasis; however, these agents are currently FDA-approved for use in patients with psoriatic arthritis.

TWO CLASSES

These five therapies can be divided into two classes according to their mechanism of action. Raptiva and Amevive are called *T-cell modulators* because they affect the activity of T cells, which are key components in the pathogenesis of psoriasis. Raptiva binds to the CD11a subunit of lymphocyte function-associated antigen (LFA)-1 and inhibits binding to intercellular adhesion molecule (ICAM)-1, blocking activation, reactivation, and trafficking of T cells. Amevive prevents the interaction between LFA-3 and the memory effector T-cell antigen CD2, thereby inhibiting T-cell activation. Enbrel, Remicade, and Humira work through a different mechanism of action: They target the cytokine tumor necrosis factor-alpha (TNF- α), which triggers the inflammatory response and cell-mediated immune responses key to the pathogenesis of psoriasis. Because these agents inhibit TNF- α activity, they are called *TNF antagonists*.

INADEQUATE RESPONSE

Although a significant percentage of patients respond well to each of these agents, the response of individual patients will vary, and no patient is guaranteed to respond to

any specific agent. Some patients respond well when first treated with biologics, but then they reach a plateau and do not achieve complete clearance. Other patients cannot

maintain clearing over time while receiving a biologic. Under such circumstances, it might be necessary to switch patients from one type of therapy to another because of lack of



response, change in response, disease progression, or contraindications.

Up to 25% of patients using a TNF antagonist do not achieve a clinical response (measured by a 50% improvement from baseline on the Psoriasis Area and Severity Index [PASI 50]) in 12 or 24 weeks of treatment.^{1,2} In addition, recent data indicate that an initial treatment response to the TNF antagonists may erode with long-term use.³⁻⁵ For example, at 10 weeks 80% of patients treated with Remicade in a phase 3 trial achieved a 75% improvement from baseline in PASI (PASI 75), but only 61% of patients showed this response by 50 weeks.¹ A similar reduction in efficacy was observed in patients receiving weekly treatment with Humira in a phase 3 trial: 80% and 64% of patients had achieved PASI 75 at 12 weeks and 60 weeks, respectively.⁴ Recent presen-

tations of Enbrel data at the 2006 meeting of the American Academy of Dermatology showed a similar trend: 63% and 51% of patients receiving Enbrel 50 mg twice weekly in a phase 3 trial achieved PASI 75 at 48 weeks and 96 weeks, respectively.^{5,6}

When patients with psoriasis do not respond adequately to TNF antagonist activity, it is important to consider switching to a treatment with a different mechanism of action, such as Raptiva. A recent presentation of six case reports illustrates the efficacy of Raptiva in patients who responded inadequately to anti-TNF therapy.⁷ These inadequate responders, whose responses plateaued at 8% affected body surface area or worsened despite treatment with Enbrel, were switched to treatment with Raptiva. These patients had histories of psoriasis ranging from 5 to 41 years and achieved clearance of their disease after switching to Raptiva.

SAFETY CONSIDERATIONS

Safety considerations may restrict the treatment choices available to patients with psoriasis. Raptiva has been shown to be safe and effective for up to 3 years in patients with chronic, moderate-to-severe plaque psoriasis.⁸ The most serious adverse reactions observed during treatment with Raptiva were serious infections, malignancies, immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, arthritis events, and psoriasis worsening and variants. Serious infections and immune-mediated thrombocytopenia have been reported during postmarketing surveillance. Physicians should follow patients for signs and symptoms of thrombocytopenia; platelet monitoring is recommended. Acellular, live, and live-attenuated vaccines should not be administered during Raptiva treatment. The most common adverse reactions associated with Raptiva were a symptom complex that included headache, chills, fever, nausea, and myalgia within 48 hours following the first two injections. These events were largely mild to moderate when a first dose of 0.7 mg/kg was given. Less than 1% of patients discontinued Raptiva treatment because of these adverse events.⁹

The use of TNF antagonists is contraindicated for patients with congestive heart failure. TNF antagonists are not recommended when a patient has a positive tuberculosis test. These and other warnings are listed in the prescribing information for these agents.¹⁰⁻¹² Use of TNF antagonists has been associated with rare cases of demyelinating disease¹³ and induction of anti-nuclear antibodies; discontinuation of use is recommended in such cases.^{11,12} These safety issues may preclude the use of the TNF antagonists in certain patients. Raptiva can be considered as a therapeutic option for these patients.

Because Raptiva's mechanism of action differs from that of the TNF antagonists, patients who are refractory to or ineligible for treatment with the TNF antagonists may benefit from switching to a psoriasis therapy that acts through T-cell modulation. Raptiva may be an effective alternative for patients who inadequately respond to treatment with TNF antagonist therapies. ●●●



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Please see www.raptiva.com or call 1-877-RAPTIVA for full prescribing information.



The Ratio of Physician Assistants to Supervising Physicians

By Jane Mast, PA-C

The physician-physician assistant (PA) relationship is best described as a team, with the physician as the captain of this team. This relationship is vital for proper supervision of physician extenders and for achieving the ultimate goal of high-quality care for our patients. Early laws dictated the number of PAs a physician could supervise. Now each state is in charge of laws regarding this ratio.

In the earlier years of the PA profession, state laws frequently limited the number of PAs a physician could supervise to a ratio of 2:1, or sometimes even 1:1. This model was designed for the primary care practice, where the majority of PAs worked at the time. As medicine has evolved and the use of PAs has increased in all areas of medicine, including specialty and hospital practice, the state laws have been modified to accommodate the new distribution of PAs among different areas of medicine. The state of Florida, where I practice, still regulates that one physician can supervise up to four PAs. The state of Connecticut, however, allows one physician to supervise up to six PAs. California specifies a 2:1 ratio at any given time. Also, sometimes ratios change if the area being served is considered medically underserved. In several states, there are no regulations regarding ratio.

It seems there is really no consensus on the best ratio of PAs to supervising physicians. Even in states that require a 2:1 ratio, there are cases in which supervision is not what it should be. Because every practice situation is different, it may be best to leave this issue to the physician-PA team itself. The American Medical Association (AMA) adopted the following statement on the issue in 1998: "Our AMA endorses the principle that the appropriate ratio of physician to physician extenders should be determined by physicians at the practice level, consistent with good medical practice, and state law where relevant."¹ The American Academy of Physician Assistants (AAPA) seems to agree with this concept: "The AAPA believes the appropriate number of PAs is



best determined at the practice level, rather than in state law."²

It is the responsibility of both the PA and the supervising physician to ensure that there is proper supervision of the PA so that patients always receive the highest quality of care. Therefore, the supervising physician and the PAs who are being supervised should make sure that the team relationship and proper supervision is maintained to the highest level. The level of this supervision should take into account the clinical competence of the PA and his or her experience. When considering a new PA-physician relationship, supervision should be discussed thoroughly so that both the PA and the physician feel comfortable with the amount of supervision that is provided.

In dermatology, where the majority of the specialty is visual in nature, it becomes vital for a close working relationship with the physician. In our practice, we have two dermatologists and two PAs. After working in dermatology for nearly 4 years, I feel confident in many areas; I also feel humbled in many areas. I feel very comfortable in our practice that when I have a question regarding any patient, one of my two supervising physicians is always present to consult with and examine the patient. This close collaboration of one-to-one supervision is what works best for both the PAs and the physicians in our practice. For other dermatology PAs with much more experience or other methods of supervision—including new technologies that allow the physicians to visualize lesions on the computer—this level of supervision

may be different. For those PAs practicing in dermatology for the first time or who are just out of school, the level of supervision and the ratio of PAs to physicians may need to be much closer, with a 1:1 ratio.

The debate about the regulation of the number of PAs a physician may supervise will undoubtedly go on. The AAPA and the AMA have developed guidelines of supervision that focus not on the numbers, but rather on the quality of the PA-physician relationship and on the quality of care provided to the patients. It is our job as professionals to ensure the highest quality of care to our patients. This includes knowing our limitations and being comfortable asking for help when it is needed. ●●●



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Brief Summary of Prescribing Information

Please see full Prescribing Information.

INDICATIONS AND USAGE RAPTIVA® (efalizumab) is indicated for the treatment of adult patients (18 years or older) with chronic relapsing to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS RAPTIVA should not be administered to patients with known hypersensitivity to RAPTIVA or any of its components.

WARNINGS Serious Infections: RAPTIVA is an immunosuppressive agent and has the potential to increase the risk of infection and reactivation latent, chronic infections. RAPTIVA should not be administered to patients with clinically important infections. Caution should be exercised when considering the use of RAPTIVA in patients with a chronic infection or history of recurrent infections. If a patient develops a serious infection, RAPTIVA should be discontinued. New infections developing during RAPTIVA treatment should be monitored. During the first 12 weeks of controlled trials, serious infections occurred in 7 of 1620 (0.4%) RAPTIVA-treated patients compared with 1 of 775 (0.1%) placebo-treated patients (see **ADVERSE REACTIONS**, Infections). Serious infections requiring hospitalization included cellulitis, pneumonia, abscess, sepsis, bronchitis, gastroenteritis, septic meningitis, Legionnaires' disease, and ectopic osteomyelitis (note: some patients had more than one infection). Postmarketing reports of serious infections include necrotizing fasciitis and tuberculous pneumonia. Bodes of sepsis with seeding of distant sites, severe pneumonia with neutropenia (ANC 900/ μ L), and worsening of infection (e.g., cellulitis, pneumonia) despite antimicrobial treatment have been observed.

Malignancies: RAPTIVA is an immunosuppressive agent. Many immunosuppressive agents have the potential to increase the risk of malignancy. The rate of malignancy is the development of malignancies is not known. Caution should be exercised when considering the use of RAPTIVA in patients at high risk for malignancy or with a history of malignancy. If a patient develops a malignancy, RAPTIVA should be discontinued (see **ADVERSE REACTIONS**, Malignancy).

Immune-Mediated Thrombocytopenia: Platelet counts of 50,000 cells per μ L were observed in 8 (0.5%) RAPTIVA-treated patients during clinical trials compared with none among the placebo-treated patients (see **ADVERSE REACTIONS**, Immune-Mediated Thrombocytopenia). Five of the 8 patients received a course of systemic steroids for thrombocytopenia. Thrombocytopenia resolved in the 7 patients receiving adequate follow-up (7 patients was lost to follow-up). Reports of severe thrombocytopenia have also been reported postmarketing. Physicians should follow patients closely for signs and symptoms of thrombocytopenia. Assessment of platelet counts is recommended during treatment with RAPTIVA (see **PRECAUTIONS**, Laboratory Tests) and RAPTIVA should be discontinued if thrombocytopenia develops.

Immune-Mediated Hemolytic Anemia: Reports of hemolytic anemia, some serious, diagnosed 4-6 months after the start of RAPTIVA treatment have been received. RAPTIVA should be discontinued if hemolytic anemia occurs.

Postleukin Worsening and Variants: Worsening of psoriasis can occur during or after discontinuation of RAPTIVA. During clinical studies, 19 of 2580 (0.7%) of RAPTIVA-treated patients had serious worsening of psoriasis during treatment ($n = 5$) or worsening post baseline after discontinuation of RAPTIVA ($n = 14$) (see **ADVERSE REACTIONS**, Adverse Events of Postleukin). In some patients these events took the form of pustular erythroderma, pustular psoriasis, or development of new plaque lesions. Some patients required hospitalization and alternative antipsoriatic therapy to manage the postleukin worsening. Patients, including those not responding to RAPTIVA treatment, should be closely observed following discontinuation of RAPTIVA, and appropriate postleukin treatment initiated as necessary.

PRECAUTIONS Arthritis Events: Infrequent new onset or recurrent severe arthritis events, including psoriatic arthritis events, have been reported in clinical trials and postmarketing. These arthritis events began while on treatment or following discontinuation of RAPTIVA and were uncommonly associated with flare of psoriasis. Patients improved after discontinuation of RAPTIVA with or without anti-arthritis therapy.

Immunosuppression: The safety and efficacy of RAPTIVA in combination with other immunosuppressive agents or phototherapy have not been evaluated. Patients receiving other immunosuppressive agents should not receive concurrent therapy with RAPTIVA because of the possibility of increased risk of infections and malignancies.

Immunizations: The safety and efficacy of vaccines administered to patients being treated with RAPTIVA have not been studied. In a small clinical study with IV administered RAPTIVA, a single dose of 0.3 mg/kg given before primary immunization with a reagent decreased the secondary immune response, and a dose of 1 mg/kg almost completely ablated it. A dose of 0.3 mg/kg IV has comparable pharmacodynamic effects to the recommended dose of 1 mg/kg SC. In chimpanzees exposed to RAPTIVA at 211 times the clinical exposure level (based on mean peak plasma levels) antibody responses were decreased following immunization with tetanus toxoid compared with untreated control animals. Acetate, live and live-attenuated vaccines should not be administered during RAPTIVA treatment.

Risk/Benefit: First dose reactions including headache, fever, nausea, and vomiting are associated with RAPTIVA treatment and are dose-level related in incidence and severity (see **ADVERSE REACTIONS**). Therefore, a conditioning dose of 0.3 mg/kg is recommended to reduce the incidence and severity of reactions associated with initial dosing (see **DOSEAGE AND ADMINISTRATION**). Cases of aseptic meningitis resulting in hospitalization have been observed in association with initial dosing (see **ADVERSE REACTIONS**, Inflammatory/Immune-Mediated Reactions).

Information for Patients: Patients should be informed that their physician may monitor platelet counts during therapy. Patients should be advised to seek immediate medical attention if they develop any of the signs and symptoms associated with severe thrombocytopenia (such as easy bleeding from the gums, bruising, or petechiae) or with severe hemolytic anemia (such as weakness, orthostatic lightheadedness, hemoglobinuria or jaundice) or with worsening of psoriasis or arthritis. Patients should also be informed that RAPTIVA is an immunosuppressant, and could increase their chances of developing an infection or a malignancy. Patients should be advised to promptly call the prescribing doctor's office if they develop any new signs of, or receive a new diagnosis of infection or malignancy while undergoing treatment with RAPTIVA.

Female patients should also be advised to notify their physicians if they become pregnant while taking RAPTIVA for within 8 weeks of discontinuing RAPTIVA and be advised of the existence of and encouraged to enroll in the RAPTIVA Pregnancy Registry. Call 1-877-RAPTIVA (1-877-727-8483) to enroll in the Registry.

If a patient or caregiver is to administer RAPTIVA, he/she should be instructed regarding injection techniques and how to measure the correct dose to ensure proper administration of RAPTIVA. Patients should be also referred to the RAPTIVA Patient Package Insert. In addition, patients should have available materials for and be instructed in the proper disposal of needles and syringes to comply with state and local laws. Patients should also be cautioned against reuse of syringes and needles.

Laboratory Tests: Assessment of platelet counts is recommended upon initiating and periodically while receiving RAPTIVA treatment. It is recommended that assessments be more frequent when initiating therapy (e.g., weekly) and may decrease in frequency with continued treatment (e.g., every 3 weeks). Severe thrombocytopenia has been observed (see **WARNINGS**, Immune-Mediated Thrombocytopenia).

Drug Interactions: No formal drug interaction studies have been performed with RAPTIVA. RAPTIVA should not be used with other immunosuppressive drugs (see **PRECAUTIONS**, Immunosuppression).

Acetate, live and live-attenuated vaccines should not be administered during RAPTIVA treatment (see **PRECAUTIONS**, Immunizations).

Drug/Laboratory Test Interactions: Increases in lymphocyte counts related to the pharmacologic mechanism of action are frequently observed during RAPTIVA treatment (see **CLINICAL PHARMACOLOGY**, Pharmacodynamics).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of RAPTIVA.

Subcutaneous injections of male and female mice with an anti-mouse CD11a antibody at up to 38 times the equivalent of the 1 mg/kg clinical dose of RAPTIVA had no adverse effects on mating, fertility, or reproduction parameters. The clinical significance of this observation is uncertain.

Genotoxicity studies were not conducted.

Pregnancy (Category C): Animal reproduction studies have not been conducted with RAPTIVA. It is also not known whether RAPTIVA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. RAPTIVA should be given to a pregnant woman only if clearly needed.

In a developmental toxicity study conducted in mice using an anti-mouse CD11a antibody at up to 38 times the equivalent of the recommended clinical dose of RAPTIVA, no evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when administered during organogenesis. No adverse effects on behavioral, reproductive, or growth parameters were observed in offspring of female mice subcutaneously treated with an anti-mouse CD11a antibody during gestation and lactation using doses 5- to 30-times the equivalent of the recommended clinical dose of RAPTIVA. At 11 weeks of age, the offspring of these females exhibited a significant reduction in their ability to mount an antibody response, which showed evidence of partial reversibility by 25 weeks of age. Animal studies, however, are not always predictive of human response, and there are no adequate and well-controlled studies in pregnant women.

Since the effects of RAPTIVA on pregnant women and fetal development, including immune system development, are not known, healthcare providers are encouraged to enroll patients who become pregnant while taking RAPTIVA for within 6 weeks of discontinuing RAPTIVA in the RAPTIVA Pregnancy Registry by calling 1-877-RAPTIVA (1-877-727-8483).

Nursing Mothers: It is not known whether RAPTIVA is excreted in human milk. An anti-mouse CD11a antibody was detected in milk samples of lactating mice exposed to anti-mouse CD11a antibody and the offspring of the exposed females exhibited significant reduction in antibody responses (see **PRECAUTIONS**, Pregnancy). Since maternal immunoglobulins are known to be present in the milk of lactating mothers, and animal data suggest the potential for adverse effects in nursing infants from RAPTIVA, a decision should be made whether to discontinue nursing while taking the drug or to discontinue the use of the drug, taking into account the importance of the drug to the mother.

RAPTIVA® (efalizumab)

Pediatric Use: The safety and efficacy of RAPTIVA (efalizumab) in pediatric patients have not been studied.

Geriatric Use: Of the 1620 patients who received RAPTIVA in controlled trials, 128 were 65 years of age, and 2 were ≥ 75 years of age. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients. Because the incidence of infections is higher in the elderly population, in general, caution should be used in treating the elderly.

ADVERSE REACTIONS The most serious adverse reactions observed during treatment with RAPTIVA were serious infections, malignancies, thrombocytopenia, hemolytic anemia, arthritis events, and postleukin worsening and variants (see **WARNINGS**).

The most common adverse reactions associated with RAPTIVA were a first dose reaction complex that included headache, chills, fever, nausea, and myalgia within two days following the first two injections. These reactions are dose-level related in incidence and severity and were largely mild to moderate in severity when a conditioning dose of 0.3 mg/kg was used as the first dose. In placebo-controlled trials, 29% of patients treated with RAPTIVA 1 mg/kg developed one or more of these symptoms following the first dose compared with 15% of patients receiving placebo. After the third dose, 4% and 2% of patients receiving RAPTIVA 1 mg/kg and placebo, respectively, experienced these symptoms. Less than 1% of patients discontinued RAPTIVA treatment because of these adverse events.

Other adverse events resulting in discontinuation of RAPTIVA treatment were postleukin (0.6%), pain (0.4%), arthritis (0.4%), and myalgia (0.3%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect RAPTIVA exposure for 2762 adult psoriasis patients (age range 18 to 75 years), including 2400 patients exposed for three months, 904 for six months, and 238 exposed for one year or more, in all controlled and uncontrolled studies. The median age of patients receiving RAPTIVA was 44 years, with 188 patients above the age of 65; 67% were men, and 89% were Caucasians. These data include patients treated at doses higher than the recommended dose of 1 mg/kg weekly.

In placebo-controlled study periods, commonly observed adverse events reported at a $\geq 2\%$ higher rate in RAPTIVA-treated patients than in placebo-treated patients were headache, infection (includes diagnosed infections and other non-specific infections), chills, nausea, pain, myalgia, flu syndrome, fever, back pain, and acne. Adverse events occurring at a rate between 1 and 2% greater in the RAPTIVA group compared to placebo were arthralgia, asthma, peripheral edema, and pruritus.

The following serious adverse reactions were observed in RAPTIVA-treated patients:

Infections: In the first 12 weeks of placebo-controlled studies, the proportion of patients with serious infection was 0.4% (21/620) in the RAPTIVA-treated group (5 of these were hospitalized, 0.3%) and 0.1% (7/775) in the placebo group (see **WARNINGS**, Serious Infections). In the complete safety data from both controlled and uncontrolled studies, the overall incidence of hospitalization for infections was 1.6 per 100 patient-years for RAPTIVA-treated patients compared with 1.2 per 100 patient-years for placebo-treated patients, including both controlled, uncontrolled, and follow-up study treatment periods. There were 27 serious infections in 2475 RAPTIVA-treated patients. These infections included cellulitis, pneumonia, abscess, sepsis, sinusitis, bronchitis, gastroenteritis, aseptic meningitis, Legionnaires' disease, septic arthritis, and ventral osteomyelitis. In controlled trials, the overall rate of infections in RAPTIVA-treated patients was 3% higher than in placebo-treated patients.

Malignancies: Among the 2762 psoriasis patients who received RAPTIVA at any dose (median duration: 8 months), 31 patients were diagnosed with 37 malignancies (see **WARNINGS**, Malignancies). The overall incidence of malignancies of any kind was 1.8 per 100 patient-years for RAPTIVA-treated patients compared with 1.6 per 100 patient-years for placebo-treated patients. Malignancies observed in the RAPTIVA-treated patients included non-melanoma skin cancer, non-cutaneous solid tumors, Hodgkin's lymphoma and non-Hodgkin's lymphoma, and malignant melanoma. The incidence of non-cutaneous solid tumors (8 in 1700 patient-years) and malignant melanoma were within the range expected for the general population.

The majority of the malignancies were non-melanoma skin cancers: 26 cases (13 basal, 13 squamous) in 20 patients (0.7% of 2762 RAPTIVA-treated patients). The incidence was comparable for RAPTIVA-treated and placebo-treated patients. However, the size of the placebo group and duration of follow-up were limited and a difference in rates of non-melanoma skin cancers cannot be excluded.

Immune-Mediated Thrombocytopenia: In the combined safety database of 2762 RAPTIVA-treated patients, there were eight occurrences (0.3%) of thrombocytopenia of $< 50,000$ cells per μ L reported (see **WARNINGS**, Immune-Mediated Thrombocytopenia). Three of the eight patients were hospitalized for thrombocytopenia, including one patient with heavy urethral bleeding; all cases were consistent with an immune-mediated thrombocytopenia. Antiplatelet antibody was evaluated in one patient and was found to be positive. Each case resulted in discontinuation of RAPTIVA, based on available platelet count measurements, the onset of platelet decline was between 6 and 12 weeks after the first dose of RAPTIVA in 5 of the 8 cases. Onset was more delayed in 3 patients, occurring as late as one year in 1 patient. In these cases, the platelet count gradually returned between 12 and 72 weeks after the first dose of RAPTIVA.

Immune-Mediated Hemolytic Anemia: Two reports of hemolytic anemia were observed in clinical trials. Additional cases were reported in the postmarketing setting. The anemia was diagnosed 4-6 months after the start of RAPTIVA, and in two serious cases the hemoglobin level decreased to 6 and 7 g/dL. RAPTIVA treatment was discontinued, erythrocyte transfusions and other therapies were administered (see **WARNINGS**, Immune-Mediated Hemolytic Anemia).

Adverse Events of Postleukin: In the combined safety database from all studies, serious postleukin adverse events occurred in 19 RAPTIVA-treated patients (0.7%) including hospitalization in 17 patients (see **WARNINGS**, Postleukin Worsening/Variants). Most of these events (14/19) occurred after discontinuation of study drug and occurred in both patients responding and not responding to RAPTIVA treatment. Serious adverse events of postleukin included pustule, erythroderma, and guttate psoriasis. During the first 12 weeks of treatment with placebo-controlled studies, the rate of postleukin adverse events (serious and non-serious) was 3.2% (52/1620) in the RAPTIVA-treated patients and 1.4% (10/715) in the placebo-treated patients.

Arthritis Events: Infrequent new onset or recurrent severe arthritis events, including psoriatic arthritis events, have been reported in clinical trials and postmarketing (see **PRECAUTIONS**, Arthritis Events).

Hypersensitivity Reactions: Symptoms associated with a hypersensitivity reaction (e.g., dyspnea, asthma, urticaria, angioedema, maculopapular rash) were evaluated by treatment group. In the first 12 weeks of the controlled clinical studies, the proportion of patients reporting at least one hypersensitivity reaction was 9% (95/1233) in the 1 mg/kg/week group and 7% (80/1113) of patients in the placebo group. Urticaria was observed in 7% of patients (101/1232) receiving RAPTIVA and 0.4% of patients (3/775) receiving placebo during the initial 12-week treatment period. Other observed adverse events in patients receiving RAPTIVA that may be indicative of hypersensitivity included laryngospasm, angioedema, erythema multiforme, asthma, and allergic drug eruptions. One patient was hospitalized with a severe skin-to-skin reaction.

Inflammatory/Immune-Mediated Reactions: In the entire RAPTIVA clinical development program of 2762 RAPTIVA-treated patients, inflammatory, potentially immune-mediated adverse events resulting in hospitalization included inflammatory arthritis (12 cases, 1.4% of patients) and interstitial pneumonitis (2 cases). One case each of the following serious adverse reactions was observed: transverse myelitis, bronchitis obliterans, aseptic meningitis, idiopathic hepatitis, sinusitis, and serous otitis hearing loss. Myelitis, eosinophilic pneumonia, resulting after discontinuation of RAPTIVA, have been reported postmarketing.

Postmarketing Experience: In postmarketing experience, other reported adverse events included toxic epidermal necrolysis and photosensitivity reactions.

Laboratory Values: In RAPTIVA-treated patients, a mean elevation in alkaline phosphatase (3 Units/L) was observed; 4% of RAPTIVA-treated patients experienced a shift to above normal values compared with 0.8% of placebo-treated patients. The clinical significance of this change is unknown. Higher numbers of RAPTIVA-treated patients experienced elevations above normal in two or more liver function tests than placebo (3.1% vs. 1.5%).

Other laboratory adverse reactions that were observed included thrombocytopenia (see **WARNINGS**, **ADVERSE REACTIONS**, Immune-Mediated Thrombocytopenia), lymphocytosis (40%) (including three cases of transient atypical lymphocytosis), and leukocytosis (25%).

Immunogenicity: In patients evaluated for antibodies to RAPTIVA after RAPTIVA treatment ended, predominantly low-titer antibodies to RAPTIVA or other protein components of the RAPTIVA drug product were detected in 6.2% (62/1003) of patients. The long-term immunogenicity of RAPTIVA is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to RAPTIVA in the ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RAPTIVA with the incidence of antibodies to other products may be misleading.

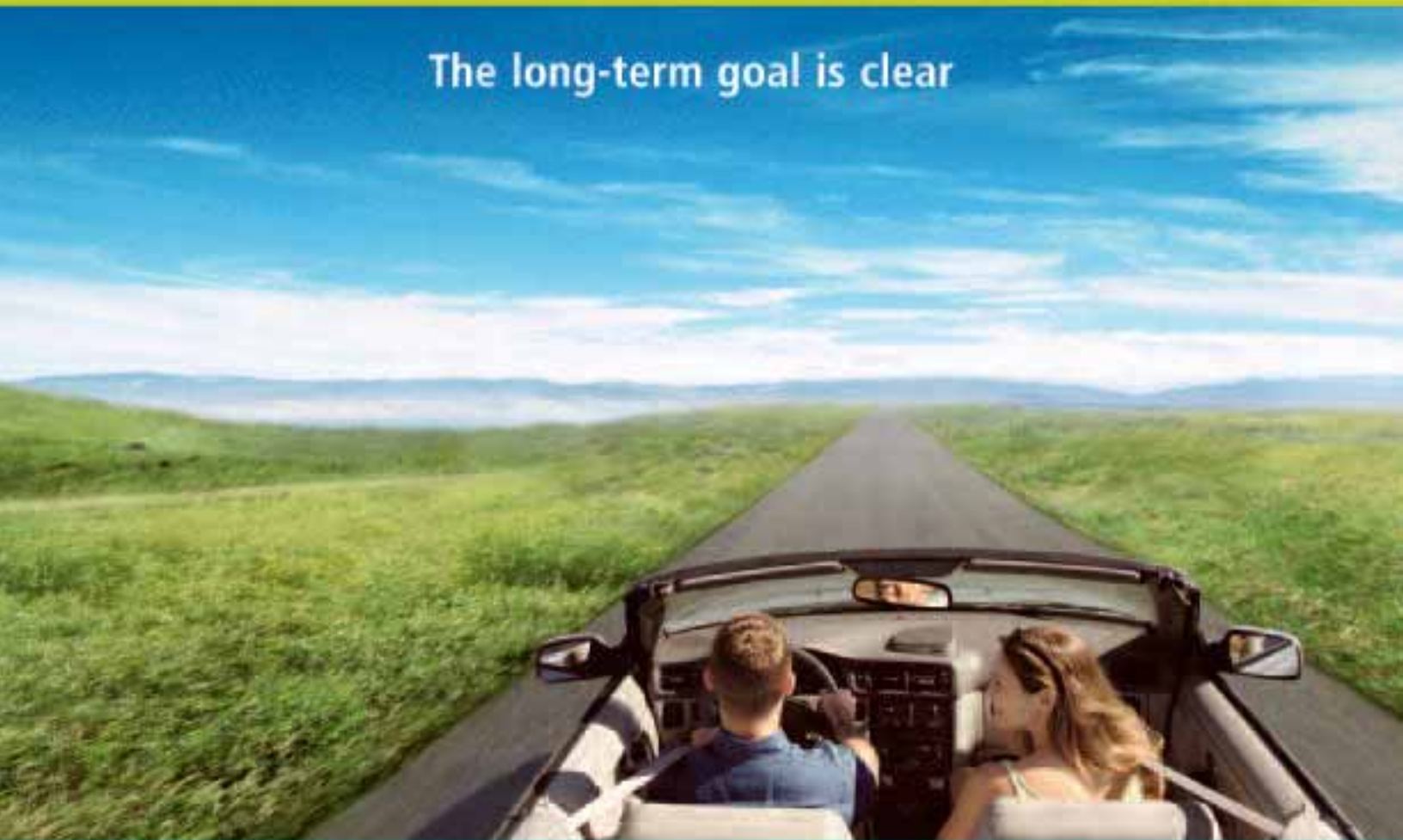
OVERDOSAGE Doses up to 4 mg/kg/week SC for 10 weeks following a conditioning (0.3 mg/kg) first dose have been administered without an observed increase in acute toxicity. The maximum administered single dose was 10 mg/kg. It has been recommended that the patient be monitored for 24-48 hours for any acute signs or symptoms of adverse reactions or effects and appropriate treatment instituted.

HOW SUPPLIED RAPTIVA® (efalizumab) is supplied as a lyophilized, sterile powder to deliver 125 mg of efalizumab per single use vial.

Each RAPTIVA carton contains four trays. Each tray contains one single-use vial designed to deliver 125 mg of efalizumab, one single-use pre-filled diluent syringe containing 1.3 mL sterile water for injection (non-USP), two 25 gauge x 5/8 inch needles, two alcohol prep pads, and a package insert with an accompanying patient information insert. The NDC number for the four administration dose pack carton is 50242-098-04.

FOR MODERATE TO SEVERE PLAQUE PSORIASIS INVOLVING THE HANDS AND FEET

The long-term goal is clear



Prescribe RAPTIVA as a first-line biologic therapy for moderate to severe plaque psoriasis involving the hands and feet

RAPTIVA® [efalizumab] is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

IMPORTANT TREATMENT CONSIDERATIONS

The most serious adverse reactions observed during treatment with RAPTIVA were serious infections, malignancies, immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, arthritis events, and psoriasis worsening and variants. Serious infections and immune-mediated thrombocytopenia have been reported during post-marketing surveillance. Physicians should follow patients for signs and symptoms of thrombocytopenia; platelet monitoring is recommended. Acellular, live, and live-attenuated vaccines should not be administered during RAPTIVA treatment. The most common adverse reactions associated with RAPTIVA were a symptom complex that included headache, chills, fever, nausea, and myalgia within 48 hours following the first 2 injections.

Please see Brief Summary of Prescribing Information on the reverse side.

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